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HHMI's Rubin Coaxes Lessons from Fly Brains

BY RICH MCMANUS

Dr. Gerald Rubin is a fly guy. This includes the *Urban Dictionary* sense of "cool and awesome"—he is vice president of the Howard Hughes Medical Institute and executive director of HHMI's Janelia Research Campus in northern Virginia and established enough to have playfully heckled NIH director Dr. Francis Collins when Collins misstated a fact during his introduction of Rubin's Wednesday Afternoon Lecture on Jan. 30. He is also a passionate student of the fly connectome: a map of every neural circuit in the brain of *Drosophila melanogaster*.

"Everything that we learn in the fly, I deeply believe will also be true in humans," said Rubin, who has studied fruit fly genetics since the 1970s.

He chose the fly as a model organism "because it is experimentally tractable, having a rather small brain of only 100,000 neurons...The small size allows for completeness. We can look at the whole brain, not just certain areas. We can define every cell type and make them genetically accessible."

Rubin had passed on other model organisms, including the worm, whose "behavior was not interesting enough."

Since starting at Janelia in 2003, Rubin, a molecular geneticist, has pursued fundamental knowledge about circuit neuroscience. The fly connectome allows scientists to "go in at any node and manipulate it—off and on—using sophisticated new tools," including optogenetics.

"What we want are general principles," he said—truths that will obtain as readily in the

SEE **RUBIN**, PAGE 4

Dr. Gerald Rubin of HHMI's Janelia campus

Guest crafter attends inn Valentine's party, p. 12.

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Alzheimer's Disease, Prion Diseases Share Similarities

BY ERIC BOCK

Dr. John Collinge

Fatal brain disorders called prion diseases might provide insight into the cause of Alzheimer's disease, said Dr. John Collinge at a recent Wednesday Afternoon Lecture Series talk in Lipsett Amphitheater.

"There are more and more similarities between what we see in prion disease and what we're seeing in Alzheimer's disease," said Collinge, professor of neurology at University College London (UCL),

SEE **COLLINGE**, PAGE 8

DARE I ASK?

Negotiator Discusses How to Navigate Conflict

BY DANA TALESNIK

Kwame Christian

The very thought of confrontation often makes our flight response kick in. We tend to dread or outright avoid potentially difficult conversations. The reality, though, is that they're inescapable. Conflict is everywhere. Luckily, there's a skill to negotiating well and it starts with looking at conflict not as a threat, but as an opportunity.

Approach any negotiation with the

SEE **NEGOTIATOR**, PAGE 6

Brady To Launch NCCIH Lecture Series on Gut Microbes, Mar. 14

The National Center for Complementary and Integrative Health will sponsor three lectures this spring on the theme of "Microbes in Our Gut: Emerging Insights on Health and Disease," as part of its Integrative Medicine Research Lecture Series.

On Thursday, Mar. 14 at 11 a.m. in Lipsett Amphitheater, Bldg. 10, Dr. Sean Brady of The Rockefeller University will inaugurate the series with his presentation "Watch Where You Step, There Is Chemistry Everywhere."

Dr. Sean Brady

Brady notes that the characterization of biologically active small molecules (natural products) produced by easily cultured bacteria has been a rewarding avenue for identifying novel therapeutics. It has also been an excellent way to gain insights into how bacteria interact with the world around them.

The traditional pure culture-based approach to studying bacterial natural products, however, has provided access only to a small fraction of the diverse metabolites encoded by environmental microbiomes. Studies suggest that in most environments, uncultured bacteria outnumber their cultured counterparts by at least two orders of magnitude.

There appears to be no easy way to culture this collection of unstudied microorganisms, but the speaker has developed culture-independent methods to circumvent this discovery bottleneck.

Brady's methods involve extraction, cloning and heterologous expression of bacterial biosynthetic gene clusters directly from environmental samples. He will discuss applying these methods to identifying new antibiotics from the global soil microbiome and metabolites encoded by the human microbiome.

Brady is Evnin and Tri-Institutional professor and head of the Laboratory of Genetically Encoded Small Molecules at Rockefeller. His research funders include NIGMS, NCCIH and NIAID.

To find out more about the event and the series (which will also be videocast), visit https://nccih.nih.gov/news/events/IMlectures.

NHLBI Cooks Up Heart-Healthy Dishes for Valentine's Day

The National Heart, Lung, and Blood Institute continued its "Hashtag Our Heart" theme for American Heart Month with cooking demonstrations on Valentine's Day. NHLBI director Dr. Gary Gibbons (l) and Dr. David Goff (r), director of NHLBI's Division of Cardiovascular Sciences, joined Eurest regional executive chef Tom Fiammetta in a special "Teaching Kitchen" set up in the Clinical Research Center atrium. They prepared "Jumpin' Jambalaya" and "Winter Crisp," heart-healthy recipes available for free at https://www.nhlbi.nih.gov/health/educational/lose_wt/eat/recipes.htm. In keeping with the 2019 theme to share heart-healthy messages widely with family and friends, attendees posted to various social media about the "Our Hearts Cook Together" event. A Facebook Live cooking demo—with "chicken and rice, two ways" on the menu—was set for later in the month.

PHOTOS: MARLEEN VAN DEN NESTE

Nominations Open for EDI 'Champions' Awards

Deadline Mar. 14

The Office of Equity, Diversity and Inclusion (EDI) is accepting nominations for the annual Harvey J. Bullock Jr. Award for Equity, Diversity and Inclusion; Yvonne Thompson Maddox Award for Equity, Diversity and Inclusion; and the Equity, Diversity and Inclusion Award of the Year.

These awards recognize NIH employees who champion EDI ideals. Requirements for each award are listed below:

• Bullock Award honors a non-supervisory employee or group of employees at grades 12 and below or the equivalent.

• Maddox Award honors a non-supervisory employee or group of employees at grades 13 and above or the equivalent.

• EDI Award of the Year recognizes executives, managers or supervisors who have made significant contributions toward furthering NIH's equity, diversity and/or inclusion efforts.

Nominations must be submitted to EDI no later than Thursday, Mar. 14. Awardees will be recognized during the 2019 NIH Director's Awards Ceremony, July 10.

For details, visit www.edi.nih.gov/consulting/outreach/edi-awards. To nominate, download www.edi.nih.gov/sites/default/files/downloads/outreach/edi-award-nomination-form-2019.pdf. You may also contact your IC awards coordinator or Dr. Anna Han, chief, Customer Outreach and Education Development Branch, at (301) 594-3357 or anna.han@nih.gov.

Leadership Education Network Encourages Women in Science

BY JANKI PATEL

Women are steadily empowering each other and narrowing the gender gap within the science field. By establishing rewarding and successful careers in science, women have risen to higher positions through hard work.

On the leadership panel are (from l) Dr. Lyric Jorgenson, deputy director, Office of Science Policy; Dr. Nakela Cook, chief of staff, NHLBI; Robin Kawazoe, deputy director, Division of Program Coordination, Planning and Strategic Initiatives, OD; Dr. Rashada Alexander, program director, NIGMS Division of Research Capacity Building; and Renate Myles, deputy director for public affairs, Office of Communications and Public Liaison, OD.

Recently a group of college students, all women, from the Public Leadership Education Network (PLEN) gathered at Natcher Conference Center for a career-focused symposium, "Preparing Women to Lead: Women in Science Careers," organized by NIH's Office of Science Policy. Attendees gained insight on how to build a successful science career from two senior scientist keynote speakers and a panel of women leaders who shared their journeys to leadership positions in biomedical research.

PLEN's mission is to increase the number of women in top leadership positions, influencing all aspects of the public policy process.

Dr. Anna María Nápoles, NIMHD scientific director, relayed her set of beliefs: "Have integrity [and] courage and help the voices that are not heard," along with "know what re-energizes your being." Her career path formed from an immigrant family background. She discussed how she has endured obstacles such as racism, sabotage and financial stress. She overcame barriers by building interpersonal emotional intelligence, staying connected with her culture and heritage and maintaining core support from her family and trustworthy peers.

Dr. Anna María Nápoles

Dr. Carrie Wolinetz, NIH associate director for science policy and acting chief of staff, began her career as a "zookeeper" and went on to become a key advisor to the NIH director. She said a "high level of personal well-being, confidence and belief in one's own abilities to succeed" will lead to where you're supposed to be in life. There is no perfect roadmap to successful careers, she noted. Workplace situations and personal life relationships should not hinder your ability to grow.

Both speakers spoke of their inspiration to enhance public health in fields underrepresented by women. They advised: "search opportunities to gain experience [volunteering on working groups or committees]," "create and expand your network with people who offer different perspectives," and ultimately, "love what you do to value your quality of life."

Dr. Carrie Wolinetz

They also said young people today need mentors who can educate, inspire and empower the next generation of women leaders by learning and sharing the core values of leadership development.

The symposium included a panel discussion with five senior NIH staff—Renate Myles, Dr. Rashada Alexander, Dr. Nakela Cook, Robin Kawazoe and Dr. Lyric Jorgenson.

Myles said she worked in various industries, promoting key messages to the public through numerous communication outlets. Her significant skill was to present complex science and communicate effectively to target audiences. She followed her passion and when facing challenges or roadblocks in her career, she found strategies for moving forward.

"Learn how to raise your visibility within the division," Myles advised. "Identify effective and trustworthy mentors who can help advance your career. Define your core network of colleagues and [work actively to become] an expert in your field."

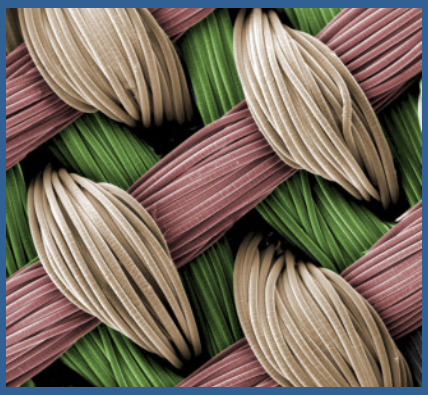
Cook offered tips for participants weaving together their own stories to shape their careers and personal development. "Be true to yourself," she said. "Know that plots can change and be flexible to their shape. Keep discovering yourself and identify your strengths and weaknesses—one day, you will inspire others."

Kawazoe emphasized that career success depends on efforts to "refine your interpersonal and communication skills; be persistent in overcoming whatever challenges you encounter; identify solutions, not just problems; be a proactive member of the team; and [not only] align yourself with people you trust and respect, but also seek out people who offer different perspectives to broaden your horizons."

Alexander's key message was to take risks and never stop being curious. "You have a lifetime of opportunities to broaden your horizon and know that you have a choice at the end of the day," she said.

Jorgenson echoed the other panelists, adding, "Be flexible, open to new opportunities [and be] a problem-solver. Challenge yourself, learn and your soul will find its way into merging college degrees and passion together."

The event concluded with a brief Q&A period, followed by a networking lunch and tour of the Clinical Center. R



ON THE COVER: *Electron microscope image provides a close-up view of a 3-D woven scaffold on which stem cells were grown.*

IMAGE: GUILAK LAB, WASHINGTON UNIVERSITY (NIH FUNDING FROM NIAMS)

The NIH Record

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NIH National Institutes of Health
Turning Discovery Into Health

Rubin

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human brain as in the fly brain.

It turns out that flies, like humans, mice and other critters, are attracted to some smells and repelled by others. This reality can be experimentally manipulated, so that "olfactory learning" can be tracked at cell level.

A fly senses odor through its antennae, which report to the antenna lobe, then to what is known as the mushroom body (calyx); in a mouse, this scheme can be expressed as nose, to olfactory bulb, to piriform cortex.

The cells activated by odor even have a name—Kenyon cells (there was no word on whether cells excited by music are known as Oberlin cells).

"There are some 2,000 papers on olfactory learning in flies," Rubin noted; it is a well-characterized phenomenon. Odor preference is mediated by dopamine signaling, which the HHMI team created tools to measure.

The Janelia scientists made some 7,000 transgenic animals that express genetic drivers to manipulate specific cell types and now have such tools for half the cell types in the fly brain. This includes 20 types of dopamine neurons.

Rubin showed short movies of flies moving from compartment to compartment within a dish as they responded to a pairing of light and dark with aversive and attractive stimuli, like Pavlov's experiments with dogs.

"They learn very quickly, with short training," Rubin noted.

To double-check whether their interpretation of neural pathway-to-behavior maps were accurate, the HHMI team used patch-clamping of specific neurons to directly measure the change in strength in the connections between specific neurons. It is such changes that store memories.

To further define the circuit boards of brain activity, the Janelia team also performs volume electron microscopy to examine synapses. Rubin said he is confident that the team is on the path to a full fly connectome by 2022.

"We had a friendly bake-off in methods," Rubin explained, pitting a milling process with use of a diamond knife. So far, they have mapped 200,000 synapses.

"This is 100 times faster than we could do the job in 2010," said Rubin. "It just needs to be 1,000 times faster."

★ ★ ★

"We think we have the tools to define circuits, but now we need to find out what they do...Is this enough? Can we understand from these datasets how the brain works?"

~DR. GERALD RUBIN

★ ★ ★

For perspective, he noted that the 156 bases that he mapped in his first published research paper in 1972 took him a year to accomplish. "In 2013, it took less than 10 nanoseconds."

Just as in large-scale genomics, Rubin said, improvements by factors of 10 are what is required.

He argued that the great pioneers of today's industrial-scale research "are certainly not the PIs [principal investigators], but the people who do the real work"—the engineer from China who developed a high-pressure freezing technique that dramatically improved the resolution of stained fly brains, without the need for cutting; the folks who do focused ion beam milling combined with scanning electron microscopy; the guy who once worked at Janelia but has now moved to Google, whose algorithms are dramatically advancing the speed with which datasets are analyzed; the teams of proofreaders who confirm the experimental work (Janelia is ramping up to 50 of them).

"But still we need to know much more," Rubin said, including information on transmitters, receptors and gap junctions that needs to be layered on top of what they can learn from the connectome.

Near the end of his talk, Rubin said his latest research interests—again, in flies—are the regulation of sleep and female-female aggression. Showing a brief clip of the 2004 film *Mean Girls*, Rubin said he told collaborator Dr. Yoshi Aso, "Yoshi, you've discovered the Mean Girl neuron!" To explain what he meant, Rubin then showed the audience a movie of female flies in a similar brawl induced by the optogenetic activation of a specific cell type in the fly brain.

"The brain is complicated," concluded Rubin. "We think we have the tools to define circuits, but now we need to find out what they do...Is this enough? Can we understand from these datasets how the brain works?"

Perhaps the answer comes from the title of a 2002 film starring Mary-Kate and Ashley Olsen: *Getting There*.

Rubin said the great pioneers of today's industrial-scale research "are certainly not the PIs, but the people who do the real work."

PHOTOS: DEBBIE ACCAME

Byrnes Named CSR Director

Dr. Noni Byrnes has been named director of the Center for Scientific Review. She had served as acting director of CSR since the retirement of former director Dr. Richard Nakamura in May 2018.

"Noni's nearly two decades of experience with NIH peer review, as well as her consummate professionalism, give me the utmost confidence that she is the best person to lead CSR through the next era of scientific discovery," said NIH director Dr. Francis Collins, who made the appointment.

Byrnes will oversee an annual budget of more than $130 million and more than 500 scientific, support and contract personnel. CSR manages the receipt and referral of all grant proposals for NIH and other parts of HHS, including the Centers for Disease Control and Prevention and the Food and Drug Administration. CSR also oversees the peer review of approximately 75 percent of the nearly 50,000 grant applications received by NIH each year.

Byrnes has worked at CSR since 2000, when she started as a scientific review officer in the enabling bioanalytical technologies study section. She also managed CSR's Review Internship Program, which transitioned bench and behavioral scientists to science administration positions.

From 2006 to 2011, she was chief of the cell biology integrated review group, and from 2012 to 2017, she served as director of the Division of Basic and Integrative Biological Sciences.

Prior to joining NIH, Byrnes worked in the pharmaceutical industry, where she conducted research to support investigational new drug submissions, served on phase III clinical trial project teams and provided oversight of contracts with clinical research organizations.

Byrnes earned her B.S. in chemistry from Allegheny College and her Ph.D. in analytical chemistry from Emory University.

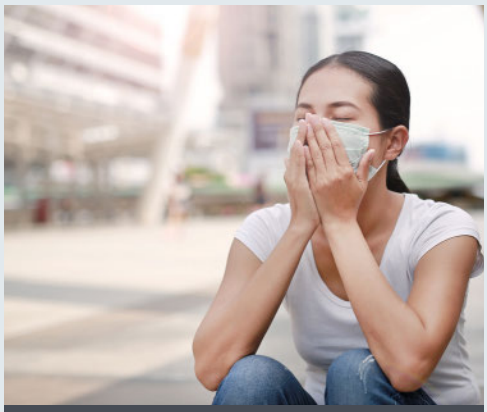
AT NASEM

Workshop Explores Interactions Between Infectious Disease, Environment

BY KELLY LENOX

Chemical exposures may prime the immune system for more extreme responses to infection, and infectious diseases influence the body's response to exposures. The need to study this interplay is urgent, according to experts who joined a National Academy of Science, Engineering and Medicine workshop held recently in Washington, D.C.

NIEHS and National Toxicology Program director Dr. Linda Birnbaum provided opening remarks, during which she emphasized that an interdisciplinary approach is crucial for gaining insights into how environmental health and infectious disease management can interact. "Exposure to environmental contaminants can alter the immune response to pathogens, and, of course, the pathogens can alter the response to the toxicants as well," she told the audience. "So we have a two-way street we have to look at."



Environmental contaminants can alter the body's response to disease-causing organisms, and vice versa.

For example, in a 1996 paper, Birnbaum reported that exposures to 2,3,7,8-tetrachlorodibenzo-p-dioxin altered the immune response of mice to the influenza virus and resulted in increased mortality. "This response has now been shown for things like air pollution, [which] can impact the response not just to influenza, but to staph and strep infections," she said.

The body's microbiomes—especially the one in the gut—are likely suspects in the search for agents of this response, due to their important roles in immunity. Dr. Rodney Dietert of Cornell University pointed out that toxicological routes of exposure involve the same entryways—such as the skin, airway and the gastrointestinal tract—that allow access to infectious agents. "They are also the physical locations where the majority of the human microbiome is housed," Dietert said. Dr. Carlos Santos-Burgoa of George Washington University underscored the point. "Somewhere we lost track of [the fact that] the microbial world and chemical world are the same world."

Several speakers addressed the complex challenges involved in studying contaminants, infections and the microbiome. Dr. Jennifer Nyland of Salisbury University discussed mercury's role in provoking an inflammatory response in parts of the body such as the brain and gut. People are exposed to different forms of mercury, both organic and inorganic. Nyland noted that while effects on the immune system are common across these forms, that is where the similarity ends. "They do not have the same level of toxicity. And they are not metabolized in your system the same way." Her viral studies in exposed mice found increased inflammatory responses and decreased anti-inflammatory action. But the responses were not seen with mercury alone; they were triggered only in the presence of a virus.

One theme of the workshop was that interdisciplinary, multidisciplinary and transdisciplinary approaches are needed to uncover the interplay between pathogens and toxicants.

Disciplines such as global health, epidemiology and immunotoxicology, as well as sectors as diverse as agriculture, housing, health care and transportation, are needed for studying pathogen–toxicant interactions.

Dr. Robert Newman of the Aspen Institute suggested that instead of approaching diseases as communicable or noncommunicable, we should view them as acute or chronic, to help bring the right combination of experts to the table.

"Despite all this interconnectedness, our responses often remain siloed in animal, human and environmental disciplines," he said.

Negotiator

CONTINUED FROM PAGE 1

belief that it's a skill we can learn and improve upon, said Kwame Christian, a lawyer and director of the American Negotiation Institute. His recent lecture in Masur Auditorium launched a new season of Deputy Director for Management seminars, organized by the NIH Training Center.

"We want to look at conflict as a signal of something that might be problematic in the underlying relationship, so we want to move toward it," with the goal of learning from and sharing with each other, said Christian, "to co-create a future that's acceptable."

Christian came prepared to address an NIH audience, armed with the basic science behind difficult conversations as well as practical tools to improve our skills.

Engaging in difficult conversations, he explained, is often a tug of war between two parts of the brain: the amygdala, responsible for emotions, and the prefrontal cortex, which regulates emotions and controls executive function and reasoning.

We have a biological response to emotional threat: our heart rate quickens, we start breathing faster. Then we start talking faster. If we're in a conversation where emotions are running high, we can't think clearly and neither person is really listening to the other's points.

In children, the prefrontal cortex isn't yet developed to regulate emotion. That's why it's futile trying to reason with a toddler having a tantrum, said Christian, who keeps learning lessons from his toddler son. "A lot of times, when we think we're having a high-level conversation [with an adult], we're really talking to their inner toddler, and that's not productive." Instead, we want the prefrontal cortex in control of the conversation.

In a strategy to address conflict, veteran mediator Christian discusses "quieting the amygdala so we can speak to the prefrontal cortex."

PHOTOS: MARLEEN VAN DEN NESTE

Now a veteran mediator, Christian admitted he used to avoid confrontation throughout his childhood. He recounted having trouble making friends as a young child in small-town Ohio, encumbered by a thick Caribbean accent. Determined not to feel lonely, he set out to make lots of friends and then didn't want to jeopardize his newfound popularity by engaging in difficult conversations.

"We're all unique, so we're all going to have different experiences that shape the way we interact with people," said Christian. "There's something we can look back on and see predictable gaps in performance; there's a gap between where we are currently and where we want to be."

Reflect on your barriers and create strategies to overcome them, he advised. But don't get so introspective that it gets in the way of embarking on meaningful conversations.

In college, a life-changing conversation would send Christian on his future career path. A mentor told him there's a difference between being liked and being respected. To succeed, he'd told Christian, find confidence in conflict.

"As you start engaging in conflict intentionally," said Christian, "you are getting better every time and, as you practice more, you're going to become more confident and more likely to do it."

The simple framework that Christian espouses is based on compassionate curiosity.

First, acknowledge the other person's emotions at the beginning and throughout the conversation. "You have a right to be upset" or "I can see why you'd feel frustrated..."

• • •

"If you engage in conflict in a meaningful way, you increase understanding and improve the relationship. Then your work product becomes better because that conflict simmering below the surface is no longer a distraction."

-KWAME CHRISTIAN

• • •

With this strategy, "we're quieting the amygdala so we can speak to the prefrontal cortex," explained Christian. "Emotions will be a legitimate barrier in these difficult conversations. Acknowledge that; get it out of the way, so you can move on to the substance later."

Next, gather information by asking open-ended questions, which allows the other person to elaborate.

"Information is the lifeblood of difficult conversations, whether it's a negotiation or a conflict," said Christian. "The more information you get, the better. But you want to make sure your tone is correct."

Asking questions with compassionate curiosity helps the other person feel safer to share the answers, said Christian. The trick is to do more listening than talking.

Keep asking questions. This keeps the person thinking and, by using the prefrontal cortex, remaining in a productive mindset. Start broadly, then get more specific, so you're gauging what's important to the person while guiding the discussion toward getting the relevant information.

Next comes the brainstorming. This is the time to restate goals and stay focused on them. Continue acknowledging emotion and asking more questions. Create a positive storyline.

Look at conflict as an opportunity to further the mission of NIH, said Christian. "If you engage in conflict in a meaningful way, you increase understanding and improve the relationship," he said. "Then your work product becomes better because that conflict simmering below the surface is no longer a distraction."

Becoming proficient at negotiating takes commitment and practice, he concluded.

"There are going to be situations where it doesn't work, where you follow everything perfectly and you don't get what you want," said Christian. "That's why giving yourself the license to fail in these conversations is important. You still want to have that interaction...you do it because the relationship is worth it and because every time you do it, you keep getting better."

Dr. Robert Carter

Carter Serves as Acting Director of NIAMS

Dr. Robert Carter has been named acting director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. He stepped into the role following the death of NIAMS director Dr. Stephen Katz last December.

Planning to continue the late director's legacy, Carter highlighted three principles that helped guide Katz: striving for fairness, working in a collegial way with other NIH institutes and centers and being a good steward of taxpayer funding.

Carter said he and all NIAMS staff will work hard to advance the institute's mission as NIH leadership prepares to conduct a nationwide search to determine the next director.

Carter has served as deputy director for NIAMS since 2008. He led policy initiatives and projects such as the NIAMS Centers evaluation working group and clinical trials working group.

He leads the Accelerating Medicines Partnership in Rheumatoid Arthritis and Lupus, a public-private partnership between government, industry, advocacy organizations and academic centers that is focusing on tissues with active disease from patients. Carter also led the development of the Back Pain Consortium, part of NIH's HEAL Initiative.

Previously, he was at the University of Alabama at Birmingham, where he was a professor of medicine and director of the division of clinical immunology and rheumatology. He also worked as a staff physician at Birmingham Veterans Affairs Medical Center.—**Greg Lavine**

IRP Launches 'Speaking of Science,' New Podcast

NIH's Intramural Research Program recently launched a new podcast, *Speaking of Science*, featuring conversations with biomedical scientists and clinicians from across NIH institutes and centers. The show will publish a new episode each month, potentially increasing in frequency as the process is refined.

In episode 1, hear NHLBI investigator Dr. Nehal Mehta discuss how treating the skin condition psoriasis can help heal heart disease. "I wanted to show that local inflammation has systemic consequences," he says.

Episode 2 finds Dr. Christine Alewine of NCI talking about new immunotoxin strategies for treating pancreatic cancer. "If ever there is something that needs someone to work on it, it would be this disease," she says.

Tune in to *Speaking of Science* at https://irp.nih.gov/podcast.

Collinge

CONTINUED FROM PAGE 1

director of the United Kingdom Medical Council prion unit, director of the UCL Institute of Prion Diseases, director of the National Hospital for Neurology and Neurosurgery's United Kingdom National Prion Clinic and visiting professor of neurology at Harvard Medical School.

A prion is an abnormal form of a naturally occurring protein that has the ability to catalyze the conversion of the normal form into the same abnormal form. Prions have been implicated in several diseases known as transmissible spongiform encephalopathies, which affect animals and humans, Collinge said. Over time, prions accumulate and damage the brain.

Symptoms of prion disease include changes in behavior, rapid onset of dementia and movement problems. Prion diseases are usually rapidly progressive and always fatal, according to the CDC. Most cases of prion disease occur randomly, Collinge explained. Certain host mutations can increase the risk of getting the disease.

The first prion disease shown to be transmissible from one person to another was kuru, a disease discovered among the Fore people of Papua New Guinea. In the 1950s, almost 2 percent of the population died from kuru annually. Collinge said it affected women and children of both sexes.

As a mark of respect, the Fore people consumed their deceased relatives' brains at funerals. Although the practice had cultural significance, it also transmitted the fatal disease. Even though the feasts ended in 1959, when the link to kuru was established, the disease continued to appear decades later in patients who had been infected earlier.

"We've seen patients with incubation periods up to 60 years, which is quite extraordinary," Collinge said.

Collinge is testing an experimental monoclonal antibody in patients with sporadic CJD.

PHOTOS: MARLEEN VAN DEN NESTE

One of the most common forms of prion disease is Creutzfeldt-Jakob disease (CJD). One type is classic, or sporadic CJD, which typically affects patients ages 65 years or older. Most patients die within 6 weeks of diagnosis. It doesn't pass from person to person. There is no risk of acquiring CJD from contact.

Another type is variant CJD, which results when a person eats meat infected with bovine spongiform encephalopathy, also known as "mad cow disease." Variant CJD typically affects patients under 30 years old.

Prion diseases can also be acquired from medical procedures, Collinge explained. Between 1958 and 1985, doctors in the U.K. gave human growth hormone (HGH) to treat almost 2,000 children with delayed growth problems. The HGH was taken from the pituitary glands of people who died.

In 1985, one patient treated with HGH from cadavers died from what's called iatrogenic CJD. Evidently, some of the HGH that patient received came from a person who had prion disease. Although treatments using human-derived growth hormone stopped more than 30 years ago, Collinge still sees patients who develop iatrogenic CJD.

In reviewing autopsy materials of patients who died long ago from iatrogenic CJD, Collinge found evidence of Alzheimer's disease. Although the patients didn't have Alzheimer's symptoms, he worried that the "seeds" of harmful proteins associated with the disease could be transmitted during medical procedures involving human tissue, particularly tissue from the central nervous system.

Collinge found some of the HGH the children received in a medical archive and confirmed the hormone had Alzheimer's proteins. Then, his lab injected the hormone into mice. Sure enough, there was "unequivocal evidence of seeding."

There's no risk of catching Alzheimer's from a person with the condition—"the concern relates only to inoculation by medical procedures," he clarified.

Doctors must continue epidemiological research to determine whether or not there's a link between surgical procedures and Alzheimer's disease. Until then, he advised physicians to consider the risks of transmission and sterilize or destroy contaminated surgical instruments.

Recently, Collinge and his lab began offering an experimental monoclonal antibody called PRN100 to patients with sporadic CJD. Mouse studies of PRN100 have been promising. Results have shown the antibody prevents abnormal proteins from attaching themselves to normal proteins and spreading. It's too soon to say whether the drug will eventually be effective treating prion diseases in humans.

"It's early yet, but I'm relieved we've gotten underway to test this drug in patients with this awful disease," Collinge said.

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Prions have been implicated in several diseases known as transmissible spongiform encephalopathies, which affect animals and humans. Over time, prions accumulate and damage the brain.

◆ ◆ ◆

Researchers Find Genetic Vulnerability to Menthol Cigarette Use

IMAGE: SAM74100/ISTOCK

A genetic variant found only in people of African descent significantly increases a smoker's preference for cigarettes containing menthol, a flavor additive. The variant of the *MRGPRX4* gene is 5 to 8 times more frequent among smokers who use menthol cigarettes than other smokers, according to an international group of researchers supported by the Food and Drug Administration and NIH. The multiethnic study is the first to look across all genes to identify genetic vulnerability to menthol cigarettes. The paper was published online in *PLoS Genetics* on Feb. 15.

Menthol provides a minty taste and a cooling or soothing sensation and plays a particularly troubling role in U.S. cigarette smoking patterns. According to the FDA, nearly 20 million people in the United States smoke menthol cigarettes, which are particularly popular among African-American smokers and teen smokers. In the U.S., 86 percent of African-American smokers use menthol cigarettes, compared to fewer than 30 percent of smokers of European descent. In addition, menthol cigarettes may be harder to quit than other cigarettes.

Although not originally the focus of the study, clues as to how menthol may reduce the irritation and harshness of smoking cigarettes were also uncovered by the researchers.

"This study sheds light on the molecular mechanisms of how menthol interacts with the body," said Dr. Andrew Griffith, scientific director and acting deputy director of NIDCD. "These results can help inform public health strategies to lower the rates of harmful cigarette smoking among groups particularly vulnerable to using menthol cigarettes."

The researchers report that 5 to 8 percent of the African-American study participants had the gene variant. None of the participants of European, Asian or Native American descent had the variant.

"While this gene variant can't explain all of the increased use of menthol cigarettes by African Americans, our findings indicate that this variant is a potentially important factor that underlies the preference for menthol cigarettes in this population," said NIDCD's Dr. Dennis Drayna. "While things like cultural factors or industry advertising practices have been a focus for understanding menthol use thus far, our findings indicate that African-specific genetic factors also need to be considered."

Study Unveils a Blueprint for Treating a Deadly Brain Tumor

In a study of mice and human brain tumors, researchers at the University of Michigan searched for new treatments by exploring the reasons why some patients with gliomas live remarkably longer than others. The results suggested that certain patients' tumor cells are less aggressive and much better at repairing DNA than others but are difficult to kill with radiation. The researchers then showed that combining radiation therapy with cancer drugs designed to block DNA repair may be an effective treatment strategy. The study was funded by NIH.

The researchers focused on low-grade gliomas that carry a disease-causing mutation in a gene called isocitrate dehydrogenase 1 (IDH1), which encodes a protein known to help cells produce energy. This mutation is found in about 50 percent of cases of primary low-grade gliomas, a common and lethal form of brain tumor. Glioma patients whose tumors have mutations in IDH1 are typically younger and live longer than those whose tumors have the normal gene. These tumors also often have mutations in genes called TP53 (a tumor suppressor gene) and ATRX (a DNA-protein complex remodeling gene).

"Every year thousands of people are diagnosed with brain cancer and have little hope for long-term survival," said Dr. Maria Castro, professor of neurosurgery at Michigan Medicine and a senior author of the paper published in *Science Translational Medicine*. "Our team's mission is to find life-saving treatments for these patients. The results from this study could be a blueprint for extending, if not saving, the lives of many patients."

"These findings have the potential to impact many younger glioma patients with low-grade tumors by either 'curing' them or extending their lives," said Dr. Jane Fountain, an NINDS program director. "The preclinical model Dr. Castro's team developed will be extremely valuable to cancer researchers. It closely mirrors the human disease."

Long Periods of Sedentary Behavior May Increase Cardiovascular Risk in Older Women

A new study has found that the longer older women sit or lay down during the course of a day—and the longer the individual periods of uninterrupted sitting—the greater their risk of cardiovascular diseases such as heart disease and stroke. But reducing their sedentary time by just an hour a day appears to lower the risk of cardiovascular diseases by 12 percent—and for heart disease alone, by a dramatic 26 percent, the research found. The study was funded by NHLBI.

"This study provides further strong evidence of a link between sedentary behavior, like sitting and laying down, which uses very little energy, and cardiovascular disease," said Dr. David Goff, director of NHLBI's Division of Cardiovascular Sciences. "Sedentary behaviors and inactivity are major risk factors for heart disease, and this research also shows that it is never too late, or too early, to move more and improve your heart health."

IMAGE: STOCKBYTE/THINKSTOCK

In this 5-year prospective study, researchers looked at more than 5,000 women ages 63 to 97 and measured both the total time they sat or laid down each day and the duration of discrete sedentary periods. The results, published Feb. 19 in the journal *Circulation*, are significant.

"Higher amounts of sedentary time and longer sedentary bouts were directly associated with cardiovascular disease," said Dr. John Bellettiere, research fellow of cardiovascular disease epidemiology at the University of California, San Diego, and lead author of the study. "Importantly, the association showed up regardless of a woman's overall health, physical function and other cardiovascular risk factors, including whether they also were engaging in moderate to vigorous physical activity."

Of the estimated 85.6 million American adults having at least one type of cardiovascular disease, which includes heart disease and stroke, 43.7 million of them are 60 or older. In fact, 67.9 percent of women between 60 and 79 years old have cardiovascular disease; heart disease is the leading cause of death among women 65 and older.

The findings, Bellettiere said, could have implications for what health officials communicate to older women about staying heart healthy. Getting up and moving, even if for just a few minutes more throughout the day, he noted, might help reduce their already-high rates of heart disease.

NIAMS Director Katz Remembered

BY GREG LAVINE

When he was a student at Bethesda-Chevy Chase High School, few could have predicted the heights he would reach as a scientist a few miles away on the NIH campus. Dr. Stephen Katz overcame early academic stumbles to eventually become director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. He passed away unexpectedly on Dec. 20, 2018, at age 77.

Katz served in NIAMS's highest office from 1995 until his death. While he rose to prominence in national and international dermatology circles during his distinguished career, he spoke candidly about his origins as a high school student with little interest in books.

"In high school and junior high school, I was a terrible student," he recalled in a video interview in 2017. "So I'm a rather ignominious graduate of this high school."

Despite that rocky start, he discovered a love of learning as an undergraduate at the University of Maryland. His studies would take him on a global journey, with stops in places such as Uganda, London and New Orleans. Katz's career included a stint in the U.S. Army at Walter Reed Medical Center during the Vietnam War before eventually landing at NIH in 1974.

Katz's NIH career began at the National Cancer Institute—first as a senior investigator and later as a lab chief—with a focus on skin and the immune system. His work contributed to major advances in our understanding of blistering skin diseases.

Research societies recognized Katz with numerous awards throughout his career. One award in particular took a place of honor in his office—the Japanese government's Order of the Rising Sun, Gold Rays with Neck Ribbon.

NIAMS director Dr. Stephen Katz

In 1995, then-NIH director Dr. Harold Varmus recruited Katz to become the second director of NIAMS. At the institute, Katz made sure his passion for dermatology did not cloud his vision. He was known for stressing the need to give all fields across the institute's broad research portfolio the support they needed.

In addition to his role at NIAMS, Katz's influence was also felt across NIH. He led more than a dozen director searches and trans-NIH committees, such as the scientific data council and the Clinical Center governing board.

"When we needed someone to provide wise advice on a complex topic (most recently, Big Data), we called Steve," wrote NIH director Dr. Francis Collins in a statement. "When we wanted someone to mentor a new member of NIH leadership, we called Steve. And he always said yes. His legacy is simply profound."

Research societies also recognized Katz's legacy, honoring him with numerous awards throughout his career. One award in particular took a place of honor in his office—the Japanese government's Order of the Rising Sun, Gold Rays with Neck Ribbon.

As a researcher, Katz was dedicated to helping develop the next generation of scientists. He took a global perspective as he mentored students from Japan, South Korea, Europe, as well as the United States. Many of those scientists are now established investigators helping to move the dermatology field forward.

Katz's focus on the future abounded at NIAMS, as he was committed to fostering training and career development opportunities in the institute's intramural and extramural research programs. In early December, he was an active participant at an annual forum for third-year K08 and K23 awardees, where he listened to and encouraged up-and-coming clinician-scientists as they pursue research independence.

"Steve's influence stretched around the world and his efforts in the lab and as a steward of public research funding have helped improve countless lives," said Dr. Robert Carter, deputy director under Katz since 2008 and currently the institute's acting director. "His legacy will live on as the scientific seeds he planted continue to bloom for years to come."

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–NIH DIRECTOR DR. FRANCIS COLLINS

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In addition to Katz's scientific pursuits, he also nurtured his creative side. He was a musical fixture at many NIH and NIAMS celebrations. He sang at a holiday event shortly before his passing.

Katz is survived by Linda, his wife of 51 years, his three children, a grandson, and numerous cousins, nieces, nephews, grandnieces and grandnephews.

A memorial service is scheduled for Friday, May 3 at 1:30 p.m. in Masur Auditorium, Bldg. 10. All are welcome.

Dr. Lance Optican

NEI's Optican Retires After 40 Years at NIH

BY LESLEY EARL

Dr. Lance Optican, chief of the section on neural modeling in NEI's Laboratory of Sensorimotor Research (LSR), will be retiring this spring. He has been a key member of the neuroscience-oriented laboratory since 1978, serving as acting lab chief from 2002 to 2006 and mentoring generations of students, fellows and colleagues along the way.

Optican occupied a unique niche at LSR: part theoretician, part engineer and part biologist. He created testable models for how neuronal circuitry in the brain controls eye movements.

"Most people build normative models—that is, as if the brain were perfectly designed, rather than imperfectly organized through evolution," said Optican's staff scientist Dr. Christian Quaia. "Lance's approach was to start from what we know about neural circuits in the brain."

Optican's journey into the eye movement field began at the California Institute of Technology, where he earned his bachelor's degree in biomedical engineering in 1972. Fascinated with the idea that one could trace electrical signals in the brain, he joined the laboratory of Dr. David Robinson, an engineer and a pioneer in the eye movement field, at Johns Hopkins University. Six years later, Optican came to NIH for a postdoctoral fellowship with Dr. F.A. Miles, and in 1982, he became a tenure-track investigator at NEI.

Early on, Optican and collaborator Dr. Barry Richmond, an experimental neurobiologist also in the LSR, took long walks around campus, just talking about how the brain works.

"We would say incredibly stupid things, and then we'd think better of them and say, 'We'd better go for another walk!'" Optican said. "That was a really exceptional time." Though it took them several years, those talks led to seminal papers that laid the groundwork for dozens of future studies relating to how neurons encode visual images.

A central focus of Optican's research over the years has been rapid eye movements, called saccades. In a condition called nystagmus, saccadic system malfunctions result in uncontrolled, oscillating eye movements that make focusing on a single point impossible. Early models for how these oscillations occur were based on simple circuits copied from engineering designs. But Optican's extensive collaborations with neurologists, neuroscientists and others helped him link specific brain circuits to nystagmus.

"I spent my career looking at data from neurophysiology and anatomy...I've been building models of eye movements—how visual information gets into the brain, how that information is used to target objects and then how the brain moves the eyes," Optican said.

After many years of filling in the gaps between theory and biology, "at some point it became clear that we knew enough about all these systems that we could influence clinical studies," Optican said. His recent work focused on creating models to help diagnose and track progression of disorders of ocular movements, including Parkinson's disease, which often leads to vision problems due to a disconnect between how the brain is moving the eye and when visual perception occurs.

Along with postdoctoral fellow Dr. Elena Pretegiani, Optican designed a quantitative test for Parkinson's severity. "In principle, all you have to do is have the patient look at a target and press a button, and by measuring their eye movements you can tell how severe his or her deficit is," Optican explained. They hope the results of a preliminary clinical study will be available in the next year.

Volunteers with RA Needed

NIAMS seeks volunteers who have rheumatoid arthritis (RA) that is well-controlled on a tumor necrosis factor (TNF) inhibitor such as Enbrel, Humira or Remicade. Doctors need to know if patients with RA in remission while taking TNF inhibitors can remain in remission without the continued use of these drugs. Compensation is provided. For more information about study 13-AR-0056, call 1-866-444-2214 (TTY 1-866-411-1010), email prpl@cc.nih.gov or visit https://go.usa.gov/xPv6a.

Vaccine Study Seeks Normal Volunteers

NIAID researchers seek healthy volunteers, 18 to 70 years old, to participate in an influenza (flu) vaccine study. Scientists are testing an investigational vaccine to determine if it is safe and if there are any side effects. There is no risk of infection since the investigational vaccine product does not contain any virus. Compensation is provided. For more information, call 1-866-833-5433 or email vaccines@nih.gov.

Adults with Knee Pain Sought

Clinical Center researchers seek 18-55 year olds with kneecap pain (patellofemoral or anterior knee pain) for a 2-visit outpatient research study. We are studying how muscle weakness around the knee may lead to changes in kneecap motion and pain. Compensation is provided. Learn how to participate by contacting the Clinical Center Office of Patient Recruitment at 1-866-444-2214 (TTY 1-866-411-1010) or prpl@cc.nih.gov. Refer to study 13-CC-0099. Read more at https://go.usa.gov/x.

NHLBI Study Recruits Volunteers

NHLBI invites volunteers ages 18-80 of African descent with or without sickle cell trait and patients with sickle cell disease to participate in a one-time visit research study. Volunteers will provide blood samples that will be used to look for a link between the PKLR gene and pyruvate kinase protein. The PKLR gene is active in the liver and in red blood cells and helps to create protein called pyruvate kinase that is essential in normal functioning of red blood cells. Compensation is provided. For more information about study 18-H-0146, call 1-866-444-2214 (TTY 1-866-411-1010) or visit https://go.usa.gov/xP8Hx.

Post-Transplant Patients Needed

NHLBI researchers are testing whether a mouth rinse containing topical dexamethasone can be used to prevent oral chronic graft vs. host disease in post-transplant patients. If you are 12 years of age or older and have received a stem cell transplant in the last 60 to 90 days, you may be eligible to participate. Study-related tests and procedures are provided at no cost. For more information, call the Office of Patient Recruitment at 1-866-444-2214 (TTY 1-866-411-1010). Read more at https://go.usa.gov/xnhak. Refer to study 07-H-0005.

First Lady Attends Inn's Valentine's Party

PHOTOS: AARON CLAMAGE

For the second year in a row, First Lady Melania Trump visited the Children's Inn at NIH on Valentine's Day. With NIH director Dr. Francis Collins and inn CEO Jennie Lucca, the First Lady was greeted warmly by kids and parents alike. The Valentine's Day party featured several tables set up in stations where small groups of children were busy assembling various crafts and handmade gifts.

With her young guides leading, the First Lady spent an afternoon filling baggies with holiday candy, coloring love-themed cards and pictures, decorating cookie boxes and making cardboard-backed candygrams. A "My Favorite Things" wall and "Home Is Where the Heart Is" map were also on display. Before leaving, Trump was presented with a necklace and flowers by one smitten young inn resident.

NIH director Dr. Francis Collins (l) and inn CEO Jennie Lucca join the inn Valentine's Day party that was attended by the First Lady. At right, she gets into the spirit of the holiday craft and gift-making activities. This is the second year in a row that she has celebrated with kids and their families at the inn.